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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,606	02/27/2004	Mary E. Brunkow	601117-109	9642

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,606	BRUNKOW ET AL.	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88,89 and 91-109* is/are pending in the application.

4a) Of the above claim(s) *97-100 and 107-109* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88,89,91-96 and 101-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's amendment of the claims filed on 19 December 2007 has been entered.

Election/Restrictions

The newly submitted claims 107-109 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the newly submitted claims are directed to a method of increasing bone mineral content in a human (new Group IV), whereas the originally claimed invention is directed to a antibody that binds to a TGF-β binding protein (original Group I).

Group I and Group IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the product as claimed can be used in a materially different method. For instance, the antibody can be used for *in vitro* assays to detect the polypeptide.

Since applicant has received an action on the merits for the originally presented invention (Group I), this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 107-109 are withdrawn

from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1-87 and 90 are cancelled. Claims 101-109 have been added. Claims 88, 89, 91-109 are pending. Claims 97-100 and 107-109 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 88, 89, 91-96 and 101-106 are under examination.

Claim ObjectionsRejections Withdrawn

The rejection of claim 88 under 35 U.S.C. 112, second paragraph, as being indefinite for reciting the term "high stringency", is withdrawn in response to Applicant's amendment of the claim to include conditions of the high stringency in the claim.

The rejection of claims 88 and 89 under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation of "alter bone density", is withdrawn in response to Applicant's amendment of the claims to recite "decrease bone mineral content".

The objection to claim 89 for a typographical error is withdrawn in response to Applicant's amendment of the claim.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The amended claims 88, 89, 91-96 and 101-106 remain rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for isolated antibodies or antigen binding fragments thereof which specifically bind to the TGF-β binding proteins encoded by the polynucleotide sequences comprising SEQ ID Nos:1, 5, 9, 11, 13, and 15, does not reasonably provide enablement for antibodies or antigen binding fragments thereof that bind to variants and fragments of the TGF-β binding proteins, for reasons of record set forth in the previous office actions.

Applicant argues that the Examiner does not appear to dispute the general facts that it is completely routine in the art to (1) make mutations or deletions in nucleotide sequences, (2) express nucleotide sequences in host cells, (3) test the expressed protein for activity, and (4) generate antibodies to proteins. Applicant argues that claims, as amended, do not reference the polypeptides encoded by a non-coding strand of SEQ ID NOs: I, 5, 9, 11, 13 and 15, and the claims now recite "decrease bone mineral content." Applicant argues that the specification discloses various routine assays well known in the art for assaying bone mineral content, and one of skill in the art could readily determine whether a protein decreases bone mineral content based on the teachings of the specification without undue experimentation. Applicant argues that the claims are directed to antibodies or antigen-binding fragments thereof that specifically bind to a polypeptide that decreases bone mineral content, and undue experimentation is not required to make the claim-recited nucleic acid molecules and encoded polypeptides.

Applicant's argument has been fully considered, but has been found to be partially persuasive.

As set forth in the previous office actions, the claims are broad in that they encompass a large genus of antibodies and antigen-binding fragments thereof that the specification fails to provided sufficient guidance how to make and use the genus.

The genus encompass: 1) an isolated antibody or antigen-binding fragment thereof which specifically binds to a polypeptide, wherein the polypeptide is encoded by a first polynucleotide capable of binding under conditions of high stringency to a second polynucleotide selected from the group consisting of fully complementary sequences to any of SEQ ID NOs: 1, 5, 7, 9, 11, 13 and 15; wherein the polypeptide retains a cysteine backbone comprising eight cysteines and retains the ability to decrease bone mineral content; 2) an isolated antibody or antigen binding fragment thereof which specifically binds to a polypeptide encoded by a polynucleotide having at least 90% identity to a polynucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 5, 9, 11, 13 and 15; wherein the polypeptide retains a cystein backbone comprising eight cysteines and retaind the ability to decrease bone mineral content; 3) a polypeptide comprising an antibody, or an antibody fragment thereof, wherein the polypeptide binds to a portion of SEQ ID NO: 2 with an affinity K_a of greater than or equal to 10^7 M^{-1}; and 4) a polypeptide comprising an antibody, or an antibody fragment thereof, wherein the polypeptide binds with an affinity K_a of greater than or equal to 10^7 M^{-1} to a polypeptide encoded by a naturally occurring polynucleotide that (i) encodes a protein that

decreases bone mineral content and (ii) is capable of hybridizing under stringent conditions to a SEQ ID NO: 1 or the complement thereof.

The claims still recite antibodies and antigen-binding fragments thereof that specifically bind to a genus of variant TGF-β binding-proteins. What Applicant has disclosed in the specification are antibodies for the TGF-β binding-proteins (e.g., BEER or SOST proteins) encoded by the polynucleotide sequences set forth in SEQ ID NOs: 1, 5, 9, 11, 13, and 15. The specification discloses that these TGF-β binding-proteins are capable to bind to BMP and prevent its binding to the receptors, and therefore, may exhibit BMP antagonistic activity and decrease bone mineral content *in vivo*. Applicant discloses a human BEER (SEQ ID NO: 1) and two variants of human BEER (V10I of SEQ ID NO: 5 and P38R of SEQ ID NO: 7), a vervet BEER (SEQ ID NO: 9), a mouse BEER (SEQ ID NO: 11), a rat BEER (SEQ ID NO: 13), and a bovine BEER (SEQ ID NO: 15). The specification, however, has not provided sufficient guidance or structure/function correlation for the genus of the variants, such as what changes can be made to the molecule so that the protein retains the ability to decrease bone mineral content. The two human BEER variants (V10I and P38R) are not sufficient for the claimed genus. While the Examiner does not dispute the general facts that techniques of mutagenesis, recombinant expression, and making antibodies are routine in the art, however, without knowing where and what mutations can be made so that the protein possesses the required activity, or does not loss the function/activity, it requires an extremely large quantity of experimentation, which is **undue**, and does not satisfy the enablement requirement set forth in the 112 first paragraph. The claims recite the

specific hybridization conditions. However, such hybridization conditions, i.e., hybridization at 45C, followed by two washes at 45-50C, allow a high degree of sequence variation (see *Current Protocols in Molecular Biology*, Copyright © 2007 by John Wiley and Sons, Inc., 1993, 2.10.1-2.10.16). The specification does not provide support that these variants exhibit the recited function/activity, i.e., decreasing bone mineral content.

With regard to a polypeptide encoded by a non-coding strand of a polynucleotide, claim 102 still encompasses such polypeptides. The specification does not provide support for any of such polypeptides which can decrease bone mineral content.

Further, the newly added claims recite antibodies and antigen-binding fragments thereof that bind to "a portion" of SEQ ID NO: 2 (claim 101). The specification does not define where and what "a portion" is. It can be a few amino acids, e.g., 1, 2, or 3 residues, etc. The claims do not even require the portion has any function/activity. The skilled artisan would not know how to use such antibodies because they can be directed to a totally different protein.

The claims recite antibodies and antigen-binding fragments thereof that have a specific affinity, e.g., K_a of greater than or equal to 10^7 M^{-1}. As cited previously, the art teaches that particular regions of a polypeptide may be critical determinants of antigenicity, and these regions can tolerate only relatively conservative substitutions or no substitutions,and in some cases, a single amino acid changes in antigen can abolish the antigen-antibody interaction entirely (see Bowie et al., Geysen et al., and Colman, references provided previously). Applicant's specification has provided little or no

guidance as to which amino acid sequences can be changed while maintaining the antibody binding affinity.

In addition, the newly added claims recite an antibody or antigen-binding fragment thereof further comprising an effector or reporter molecule, and these molecules can be any one of those recited in claim 104, e.g., antineoplastic agents, toxins, biologically active proteins and fragments thereof, nucleic acids and fragments thereof, etc. These molecules have diverse structure and function. There is no guidance in the specification as to how to make and use antibodies which further comprise these molecules, for example, how to use an anti-TGF-β binding protein antibody comprising an anti-tumor agent, or how to use an anti-TGF-β binding protein antibody comprising any nucleic acid?

Since detailed information regarding the correlation of structure and function is lacking, it is unpredictable as to which encoding variations, if any, meet the limitations of the claims. Therefore, it would require the artisan to use the current invention as a starting point for further experimentation. The scope of patent protection sought by Applicant as defined by the claim fails to correlate reasonably with the scope of enabling disclosure set forth in the specification. Therefore, the enablement requirement is not fulfilled.

Double Patenting

The amended claims 88, 89, 91-100 remain rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-8 of U. S. Patent No: 6,803,453, for reasons set forth in the previous office actions.

Applicant has requested that the rejection be held in abeyance until there is an indication of allowable subject mater, and at that time, Applicant will consider filing a terminal disclaimer.

New Grounds of Objections/Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 101 and 103-106 are rejected under 35 U.S.C. 102(e) as being anticipated by Queen et al. (U. S. Patent No: 6,180,370 B1, which has a priority filing on 28 December 1988).

The claims are directed to a polypeptide comprising an antibody, e. g., murine mAbs, human mAbs, and humanized mAbs, or an antibody fragment thereof, e. g., $F(ab')_2$, $F(ab)_2$, Fab', Fab, and Fv; wherein the polypeptide binds to a portion of SEQ ID NO: 2 with an affinity Ka of greater than or equal to i07 M-~ (claims 101, 105, 106);

wherein the polypeptide further comprising an effector or reporter molecule selected from the group as listed in claim 104 (claims 103, 104).

The '370 patent teaches humanized immunoglobulins and antigen-biding fragments thereof, e.g., Fab, Fv, and $(Fab')_2$, that have an affinity of Ka greater than 10^7 M^{-1} (col. 58, table 6; col. 11, lines 21-37). The '370 patent teaches that the antibodies may be labeled, e.g., with enzymes, radionucleotides, and fluors (col. 20, lines 21-31). Since the claims only require the binding to a portion of SEQ ID NO: 2, the antibodies taught in the '370 patent meet the limitations of the instant antibodies. Therefore, the '370 patent anticipates the instant claims.

Claim Objections

Claim 102 is objected to because of the following informalities: The word "a" should be deleted from the phrase "to a SEQ ID NO: 1".

Appropriate correction is required.

Conclusion

NO CLAIM IS ALLOWED.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
February 17, 2008

/Elizabeth C. Kemmerer/

Primary Examiner, Art Unit 1646